UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,699	09/28/2006	Peter Meikle	A20-079	2317

28156 7590 12/02/2009

COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGE PORT, CT 06605-1601

EXAMINER	
XU, XIAOYUN	
ART UNIT	PAPER NUMBER
1797	
MAIL DATE	DELIVERY MODE
12/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,699	MEIKLE ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment and RCE filed on 10/21/2009 has been entered and fully considered. Claim 3 is canceled. Claims 1 and 4-27 are pending, of which Claims 1, 17 and 23 are amended.

Response to Amendment

2. In response to amendment, the examiner maintains rejection over the prior art established in the previous Office action.

Claim Rejections - 35 USC § 102

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. **Claims 1, 4-9** are rejected under 35 U.S.C. 102(b) as being anticipated by Fujiwaki (Brain & Development, 2002, IDS) (Fujiwaki).

In regard to Claim 1, Fujiwaki teaches a method of assessing a Lysosomal Storage Disorder (LSD) status of an individual. The method comprises the steps of

taking a tissue (skin fibroblasts) from the individual (see page 171, left col. 2nd paragraph);

estimating a level in the sample of each of three or more compounds indicators (sphingomyelin, monohexosylceramide, and ceramide) each of these three compounds is the indicative of the level of respective lipid containing storage associated compounds (see page 171, left col. 5th paragraph);

calculating an LSD index number for every one LSD using ratios of ceramide/sphingomyelin, ceramide/monohexosylceramide and monohexosylceramide/sphingomyelin intensities; and

comparing the LSD index numbers of the sample with a standard (control sample) to provide an assessment of the LSD status of the individual (see page 171, left col. 5th paragraph). Fujiwaki shows that for Farbar disease patient, the ceramide/sphingomyelin and ceramide/monohexosylceramide intensity ratios are remarkably high, and monohexosylceramide/sphingomyelin is normal (see page 171,

left col. 5th paragraph, Figure 2 A, B, C); and for Gaucher disease patient, the ratio of monohexosylceramide/sphingomyelin intensity is high, and ceramide/sphingomyelin and ceramide/monohexosylceramide intensity ratios are normal (see page 171, left col. 6th paragraph, Figure 2 A, B, C).

In regard to Claim 4, Fujiwaki teaches that the storage associated compounds are selected from the group compounds consisting of phospholipids (sphingomyelin) and glycolipids (glucosylceramide) (see abstract).

In regard to Claim 5, Fujiwaki selects glucosylceramide which is a glycosphingolipid as the glycolipid indicator (see abstract).

In regard to Claims 6 and 7, Fujiwaki selects sphingomyelins as the storage associated compounds (see page 171, left col., 4th paragraph).

In regard to Claims 8 and 9, Fujiwaki teaches that DE MALDI-TOF-MS is used for analyzing the lipids (see page 171, left col., 3rd paragraph).

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. **Claims 10-16, 23, 25** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujiwaki in view of Whitfield (Molecular Genetics and Metabolism, 2002, IDS) (Whitefield).

In regard to Claim 10, Fujiwaki teaches a method of assessing and screening an LSDs status of an individual by measuring storage associated compounds selected from group of compounds consisting of phospholipids and glycolipids. Fujiwaki does not specifically teach using ESI-MS/MS to measure storage associated lipids in the method. Whitfield teaches using ESI-MS/MS to measure storage associated compounds which are glycolipids (see page 48, the bottom paragraph). ESI-MS/MS provides more accurate measurement than DE MALDI-TOF-MS due to the fragments measurement in MS/MS. At the time of the invention it would have been obvious to one of ordinary skill in the art to use ESI-MS/MS to measure storage associated lipids as taught by Whitfield in Fujiwaki's method with reasonable expectation that this would improve the accuracy

of the measurement of storage associated lipids, because tandem MS/MS spectroscopy provides detailed information on the structure of the compounds.

In regard to Claim 11, Whitfield selects glucosylceramide (GC) as storage associated compound which increases in Gaucher disease patients (see page 50, left col. 2nd paragraph, Figure 3A, B). Whitfield also selects lactosylceramide (LC) as storage associated compound which decreases in Gaucher disease patients (see page 51, right col. 1st paragraph, Figure 3C). Whitfield calculates the ratio of glucosyl-ceramide/lactosylceramide. The GC/LC ratio further improves the ability to discriminate between Gaucher and unaffected population (see page 51, right col. 1st paragraph, Figure 3D). At the time of the invention it would have been obvious to one of ordinary skill in the art to modify Fujiwaki's method by measuring LC in addition to GC and calculate the ratio of GC/LC as taught by Whitfield with reasonable expectation that this would further improve the ability to discriminate between Gaucher and unaffected population.

In regard to Claim 12, Whitfield uses plasma sample which is derived from whole blood (see page 47, left col. last paragraph and right col. 1st paragraph). At the time of the invention it would have been obvious to one of ordinary skill in the art to use plasma sample in Fujiwaki's method with reasonable expectation that the plasma sample will provide storage associated lipids based on teaching of Whitfield.

In regard to Claim 13, Whitfield discloses that the samples are obtained from patients group who are 2 month to 50 years of age and a control group who are 1 month to 15 years age (see page 47, left col. last paragraph and right col. 1st paragraph). At the time of the invention it would have been obvious to one of ordinary skill in the art to use infant plasma sample in Fujiwaki's method with reasonable expectation that the infant plasma sample will help diagnose LSD in infant based on teaching of Whitfield.

In regard to Claims 14-16, Whitfield teaches that in Gaucher disease there is a significant variation in the clinical phenotype among patients and as a result prognostic evaluation of affected individuals is difficult (see page 53, left col. 2nd paragraph). Whitfield further teaches that highly significant correlations are found between the level of LSD related protein (LAMP-1 and saposin C) and the calculated LSD indicator ratio of

GC/LC (see page 51, right col. 3rd paragraph, Figure 4B). Whitfield teaches that the use of specific biochemical makers such as GC/LC, which may relate to the observed pathology in Gaucher disease could improve our ability to predict the disease progression (see page 53, left col. 2nd paragraph). At the time of the invention it would have been obvious to one of ordinary skill in the art to modify Fujiwaki's method by measuring the level of GC and LC and calculating the ratio of GC/LC as taught by Whitfield in order to provide a good prediction about the progress of the LSD before the symptom becomes apparent.

In regard to Claims 23 and 25, Applicant is advised that the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. (see KSR, 550 U.S. at ___, 82 USPQ2d at 1395) (see MPEP 2143). In that regard, Fujiwaki teaches comparing SM with GC for assessing Gaucher disease (see page 171, left col. 6th paragraph). Whitfield teaches comparing LC with GC for assessing Gaucher disease (see page 51, right col. 3rd paragraph). One of ordinary skill in the art could have combined the two methods as taught by Fujiwaki and Whitfield. In the combination (SM and LC compare with GC), each method (SM/GC or LC/GC) merely performs the same function (assess the status of Gaucher disease) as it does separately. One of ordinary skill in the art would have recognized that the result of the combination were predictable.

7. **Claims 17-22** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujiwaki in view of Cable (Neurology, 1982, IDS) (Cable).

In regard to Claim 17, Fujiwaki teaches measuring the level of ceramide (Cer) selected from the first compound group, and measuring glucosylceramide (GC) and sphingomyelin (SM) selected from the second compound group to assess and screen the status of LSDs (see page 171, left col. 5th paragraph). Fujiwaki is silent on assessing Fabry as one of LSDs. Cable teaches measuring the level of trihexoceramide (CTH) and lactosyl ceramide (LC) from the first compound group to assess Fabry

disease (page see page 1142, Figure 3). Cable is silent on measuring the compound selected from the second compound group. Applicant is advised that the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. (see *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395) (see MPEP 2143). In that regard, one of ordinary skill in the art could have combined the above two methods as taught by Fujiwaki and Cable. In the combination, each method merely performs the same function as it does separately. One of ordinary skill in the art would have recognized that the result of the combination were predictable. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Fujiwaki and Cable to obtain the invention as specified in claim 17.

In regard to Claims 18 and 19, the combined teaching of Fujiwaki and Cable would measure the level of ceramide (Cer), trihexosyceramide (CTH), and lactosyl ceramide (LC) selected from the first compound group, to compare with sphingomyelin (SM) or glucosylceramide (GC) selected from the second compound group to assess and screen the status of Fabry.

In regard to Claims 20 and 21, the combined teaching of Fujiwaki and Cable would teach CTH and LC compare to SM (C24:0). Fujiwaki teaches SM is C24:0 species and Cer is C22:0 species (see Table 1). Cable is silent on the length of CTH and LC. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been obvious to one of ordinary skill in the art to select the optimum length of the storage associated lipids to measure in assessing the status of LSD.

In regard to Claim 22, the applicant is advised that the Supreme Court recently clarified that a claim can be proved obvious merely by showing that the combination of known elements was obvious to try. In this regard, the Supreme Court explained that, "[w]hen there is a design need or market pressure to solve a problem and there are a

finite number of identified, predictable solutions, a person of ordinary skill in the art has a good reason to pursue the known options within his or her technical grasp." An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of the case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. The combination of familiar elements is likely to be obvious when it does no more than yield predictable results. See *KSR Int'l v. Teleflex Inc.*, 127 Sup. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007) (see MPEP § 2143). In this regard, Fujiwaki teaches indexes calculated according to the formula: GC/SM (Monohexosylceramide includes glucosylceramide (GC)) (see page 171 left col. 6th paragraph, Figure 2C). Cable teaches indexes calculated according to the formula: CTH/GC or LC/GC (see peak # 5, 4, and 2 in Figure 3 and ratio of CTH/GC in table). One of ordinary skill in the art would have been able to combine the formulas taught by Fujiwaki and Cable to derive the formula: LC*CTH/GC* SM as in the instant claim. The combined index does no more than yielding the predicted results.

8. **Claims 24 and 26** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujiwaki in view of Whitfield as applied to Claims 10-16, 23, 25 above, and further in view of Aerts (Journal of Inherited Metabolic Disease, 1993, vol. 16, page 288-291) (Aerts).

In regard to Claims 24 and 26, the combined methods of Fujiwaki and Whitfield teach comparing SM and LC with GC. However, Fujiwaki and Whitfield are silent on measuring the level of Cer in assessing the status of Gaucher disease. Aerts teaches that Gaucher disease is owing to the deficiency in glucocerebrosidase activity, changes in cellular concentration of the substrate (glucosylceramide) and product (ceramide) of the reaction can be expected to occur (page 290, lines 12-15). Based on Aerts' teaching, one of ordinary skill in the art would have derive that since Gaucher patients have glucocerebrosidase deficiency, their glucosylceramide (GC) level would increase and their ceramide (Cer) level would decrease. Therefore, it would have been obvious for one of ordinary skill in the art to include the level of Cer as Gaucher disease indicator in the combined method of Fujiwaki and Whitfield to compare SM and LC with

Cer and/or GC, with reasonable expectation that the decreased level of Cer would serve as an indicator of the severity of Gaucher disease.

9. **Claim 27** is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitfield in view of Fujiwaki.

In regard to Claim 27, Whitfield teaches a method of developing a LSD diagnostic method. The method comprises the steps of

taking a first group of LSD samples (plasma sample) one each from a 30 patients with Gaucher disease (see page 47 left col. Last paragraph);

taking a second group of control sample (plasma sample) one each from 11 healthy adults (see page 47, right col. 1st paragraph);

the sample being of body fluid (plasma) of the individual, an LSD group of individual with Gaucher disease;

interrogating the level of GC and LC in the plasma by mass spectrometry for the group of Gaucher patients and the group of healthy control (see page 48 *Quantification of Plasma Glycolipids,* Table 1; page 49 left col. 1-3 paragraph);

the lipid containing storage associated compounds selected from the class of compounds consisting of the group glycolipids (GC and LC) (see Table 1);

comparing the patient's levels with control levels identifying a first group of lipid containing storage associated compound (GC) which are shown as having increased levels of indicators in the LSD group compared to the control group (see page 50, left col. 2nd paragraph, Figure 3A, B);

identifying a second group of lipid containing storage associated compounds (LC) which are shown as having decreased levels of indicators in the LSD group compared to the control group (see page 51, right col. 1st paragraph, Figure 3C);

formulating a combination of two or more of the indicators (GC/LC) by which to calculate an index number to distinguish LSD samples from control samples (see page 51, right col. 3rd paragraph, Figure 3D);

preparing a standard being a scale of index numbers (GC/LC) reflective of the severity of the LSD. Whitfield shows correlation between GC/LC values and activity of LSD related protein, LAMP-1 and Saposin C (see page 51, right col. 3rd paragraph,

Figure 4 A, B). The correlation provides a scale of index number reflective of the severity of the LSD.

Whitfield is silent on selecting the class of compounds consisting of phospholipids. Fujiwaki teaches measuring the level of storage associated compounds consisting of phospholipids (sphingomyelin) and glycolipids (glucosylceramide) in diagnosing Gaucher disease (see page 171, left col. 6th paragraph, Table 1). At the time of the invention, it would have been obvious to one of ordinary skill in the art to include sphingomyelin taught by Fujiwaki in the diagnostic method of Whitfield with reasonable expectation that this would provide a second indicator for the diagnosis of Gaucher disease.

Whitfield is silent on formulating a combination of three or more of the indicators by which to calculate an index number to distinguish LSD samples from control samples. Fujiwaki teaches calculating an LSD index number using ratio of ceramide/sphingomyelin and ceramide/monohexosylceramide intensities; and comparing the LSD index number of the sample with a standard (control sample) to provide an assessment of the LSD status of the individual (see page 171, left col. 5th paragraph). Fujiwaki shows that for Farbar disease patient, the ceramide/sphingomyelin and ceramide/monohexosylceramide intensity ratios are remarkably high (see page 171, left col. 5th paragraph, Figure 2A, B), and for Gaucher disease patient, the ratio of monohexosylceramide/sphingomyelin intensity is high (see page 171, left col. 6th paragraph, Figure 1C). That suggests that the use of two ratios is better than the use of one ratio, for distinguish Farbar disease from Gaucher disease. At the time of the invention it would have been obvious to one of ordinary skill in the art to formulate a combination of three or more of the indicators as taught by Fujiwaki in Whifield's method, because Fujiwaki shows that the use of two ratios is better than the use of one ratio.

Response to Arguments

10. Applicant's arguments filed 10/21/2009 have been fully considered but they are not persuasive.

The applicants argue that "Fujiwaki does not calculate an index number derived from three different compound indicators. Nor is there even an oblique suggestion in Fujiwaki of calculating such an index number. In Fujiwaki, two ratios are presented for the individual affected by Faber desease (FD), each indicative of the level of ceramide, the two ratios each having a different internal control. They each measure the same thing, namely ceramide levels." The examiner respectfully disagrees with the applicant's argument. Fujiwaki teaches calculating an LSD index number using ratio of ceramide/sphingomyelin, ceramide/monohexosylceramide and monohexosylceramide/ sphingomyelin intensities; and comparing the LSD index number of the sample with a standard (control sample) to provide an assessment of the LSD status of the individual (see page 171, left col. 5th paragraph, Figure 2 A, B, C). Therefore, Fujiwaki envisages calculating an index number using all three compound indicators (ceramide, sphingomyelin and monohexosylceramide). Fujiwaki shows that for Farbar disease patient, the ceramide/sphingomyelin and ceramide/monohexosylceramide intensity are remarkably high, and monohexosylceramide/sphingomyelin ratio is normal (see page 171, left col. 5th paragraph, Figure 2 A, B, C), and for Gaucher disease patient, the ratio of monohexosylceramide/sphingomyelin intensity is high, and the ceramide/sphingomyelin and ceramide/monohexosylceramide intensity are normal (see page 171, left col. 6th paragraph, Figure 2 A, B, C). That suggests that the use of index number derived from ceramide, sphingomyelin and monohexosylceramide is a good indicator for distinguishing Farbar disease and Gaucher disease from other LSD diseases. This is consistent with the purpose of the instant application -- provide a better discrimination of LSD disease.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

11/28/2009

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

RX